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Accumulation and disappearance of lactate in a fetus with a hemochorial placenta. The role of placental transfer and fetal metabolism.

W. Moll and E. Kastendieck

Lactic acid accumulates in the fetal body during hypoxic periods (fetogenic acidosis) and disappears during normoxic periods. In sheep and other species with an epitheliochorial placenta which is virtually impermeable for lactate [12] the rate of accumulation and disappearance seems to be determined only by the rate of fetal lactate production and utilisation. In man, however, and other species with a hemochorial placenta which is well permeable for lactate [4, 6] the placental transfer is expected to slow down the rate of accumulation of lactate and to speed up the rate of disappearance. Thus, the rate of accumulation and disappearance of lactate in a fetus with a hemochorial placenta is determined by the rate of both fetal metabolism and placental transfer.

It is the aim of this paper to describe the rate of accumulation during and the rate of disappearance after hypoxia in a species with a hemochorial placenta (guinea-pig) and to assess, for constant maternal lactate concentrations, the role of placental transfer and fetal metabolism. Special reference is given to the correlation between the rates of lactate metabolism and fetal-arterial oxygen concentration.

1 Methods

Pregnant guinea-pigs near term were used (maternal weight: 1.0 kg (SD = 0.15); fetal weight: 80 g (SD = 20); placental weight: 4 g (SD = 0.6). The preparation is shown in Fig. 1. It allowed us to measure and to adjust the maternal placental blood flow in a wide range, to induce in this way hypoxia and normoxia in the fetus, and to draw samples from the maternal arterial, maternal uterovenous, and fetal arterial blood in these conditions. In the blood samples we measured the lactate concentration (using the lactate dehydrogenase method), pH, pCO_2 and pO_2 with commercial electrodes, the hematocrit, and the hemoglobin concentration according to the cyanmethemoglobin method. From the data, the plasma lactate concentration was calculated as described in a previous paper [6]. The O_2 saturation and the O_2 concentration were derived from the pO_2 using the O_2 dissociation curves for fetal and adult blood of the guinea-pig [3]. The base deficit was determined for the extracellular space [10], corrected for oxygenated blood. From the uteroplacental blood flow and the arteriovenous concentration differences the placental transfer of O_2 and lactate was determined.

Curriculum vitae

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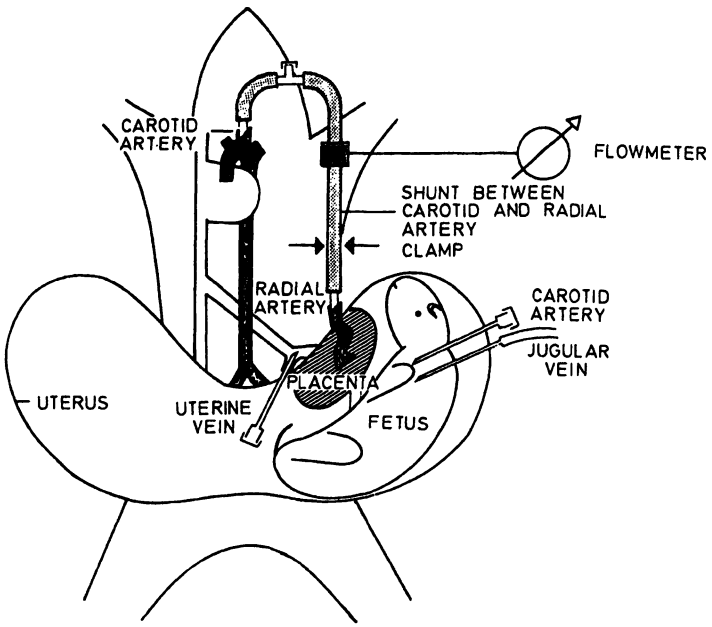

Fig. 1. Preparation of the pregnant guinea-pig

The maternal carotid artery of the anaesthetized animal is connected with the final, dilated part of an uteroplacental artery via a silastic tube and an electromagnetic flowmeter as described by (5). In this way, the limiting flow resistance is bypassed and the uteroplacental blood flow can be adjusted in a wide range using a clamp. The other uteroplacental arteries were tied. An additional catheter was inserted into the maternal uterine vein. After making a 3 cm incision in the uterus and in the fetal membranes the fetal head was partially exposed, fixed to the uterine muscle by suture and covered with thin plastic sheets. The fetal carotid artery and the jugular vein were cannulated with small polyvinyl tubes. Blood samples of 200–300 μl at the most were drawn from the fetus; the blood was replaced by maternal arterial blood. The anaesthesia and the temperature control were performed as described by (6).

(The metabolism of the uterine muscle and the placenta was neglected). The lactate transfer (T) across the placenta was also derived from the concentration difference of lactate was also derived from the concentration difference of lactate in fetal and maternal arterial plasma (Δc) and the placental clearance (C):

$$T = \Delta c \cdot C \qquad (1)$$

The placental permeability of lactate is 25 ml/h per g of placental tissue in the guinea-pig [6]; according to this value the placental clearance is calculated to be 1.2 ml/min for normal placental plasma flow and 1.0 ml/min for reduced maternal plasma flow (2 ml/min) when the placental weight is 4 g. This can be shown by rearranging eq. [2] in [6] (see p. 170 in [6]).

2 Results and discussion

2.1 Accumulation, placental transfer and production of lactic acid during a hypoxic period.

The uteroplacental blood flow was reduced from 17 to about 3 ml/min for 10 min in 9 animals. As shown in Fig. 2, hypoxia occurred in the fetus under these conditions: **The mean uterine O_2 uptake fell from 0.7 to 0.2 ml/min, fetal arterial O_2 concentration dropped from 10 to 2 ml/100 ml. The lactate concentration in the fetal arterial plasma and the base deficit in the extracellular space increased.**

In Fig. 3, the single values of the increase with time of the lactate concentration in the arterial plasma and of the base deficit in the extracellular space occurring during the hypoxic period are related to the fetal arterial oxygen concentration.

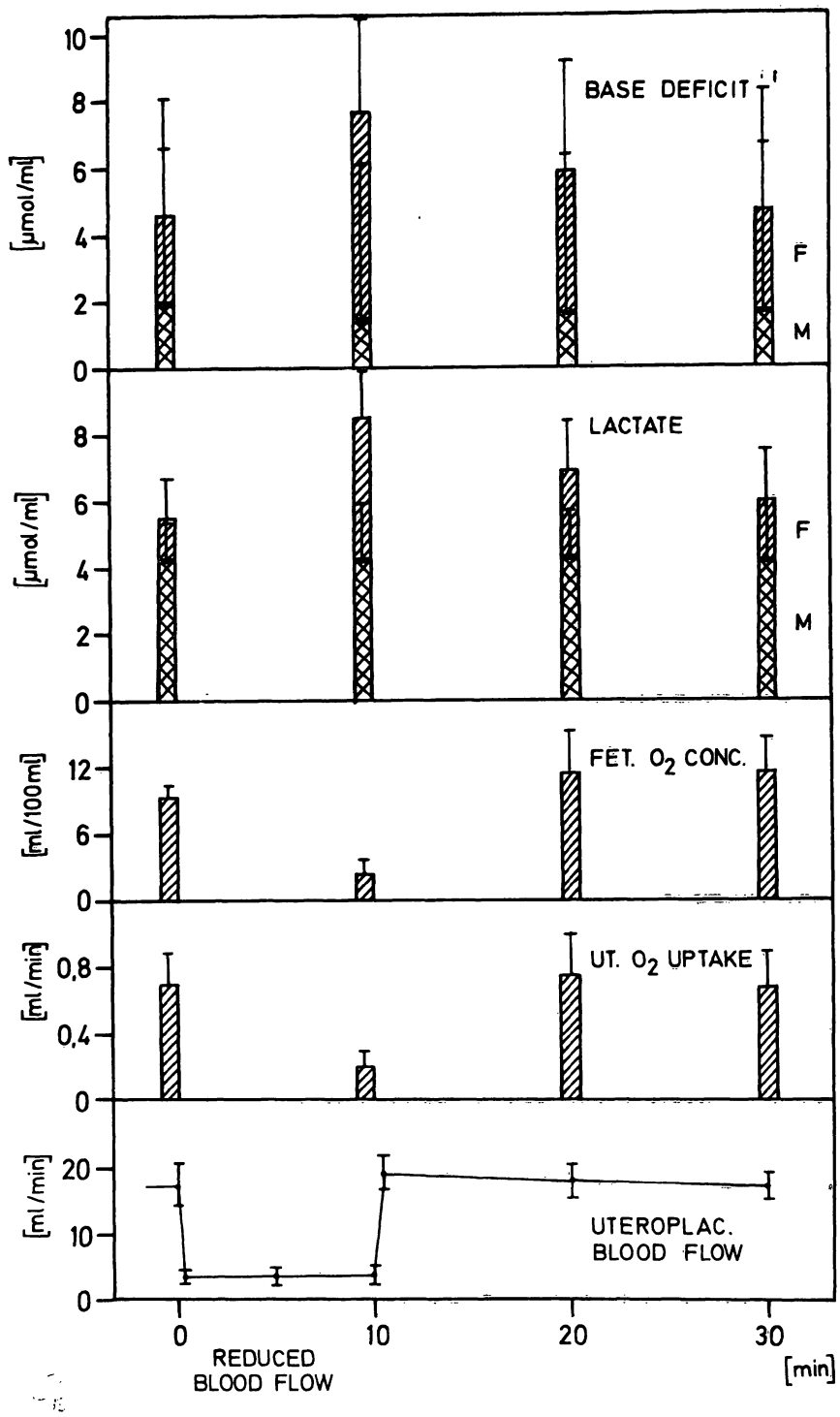

Fig. 2. Base deficit in the extracellular space of the fetus (whole columne, F) and the mother (douple hatched columne, M), lactate concentration in fetal (F) and maternal (M) arterial plasma, fetal arterial O_2 concentration, uterine O_2 uptake and uteroplacental blood flow during the experiment.

The bars indicate the standard deviation of the mean (n = 9).

The lactate concentration increase was equivalent to the increase of the base deficit. As shown by Fig. 3, the lactate accumulated when the oxygen concentration dropped to a value below 5 ml/100 ml, i.e. 25% oxygen saturation. This is the critical oxygen saturation below which the oxygen consumption of the fetus was reported to decrease significantly [1, 8]. The rate of lactate concen-

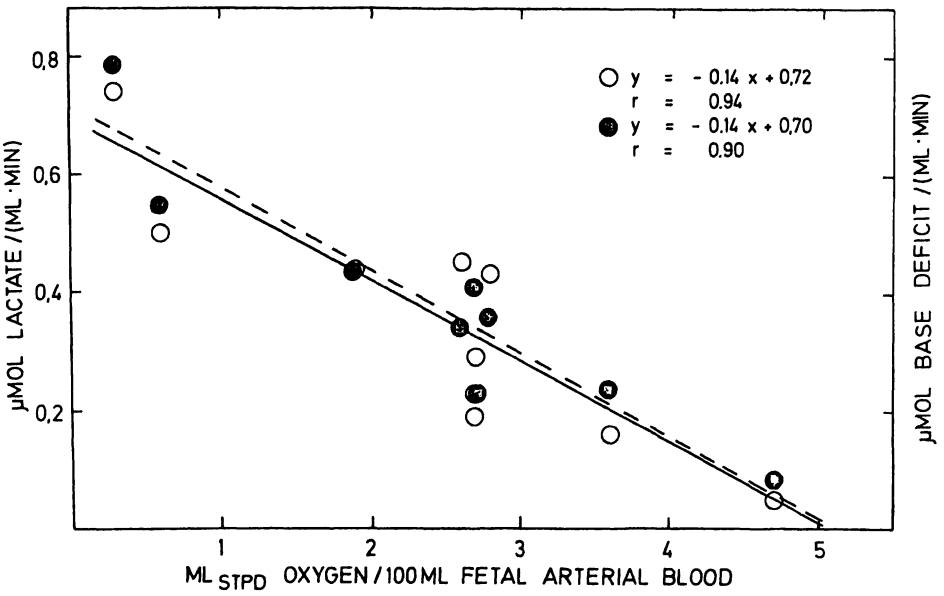

Fig. 3. Rise of lactate concentration in fetal arterial plasma (solid line, closed circles), and the base deficit in the extracellular space (broken line, open circles) related to the oxygen concentration in fetal arterial blood (n = 9).

tration increase reached a maximum value of about 0.7 µmol/(ml · min) when the fetal arterial oxygen concentration was virtually zero. The maximum speed of lactate concentration increase found in this study is about the same as reported for the lamb near term [2] but higher than found for the human fetus of the 5.–6. month (0.3 µmol/(ml · min) according to [9]).

The mean lactate concentration in the fetal body was found to be about 60% of the plasma concentration in the guinea-pig according to measurements in the fetal plasma and the homogenized fetal body (see Fig. 4). Thus, the rate of increase of the lactate concentration in the fetal body (the **lactate accumulation**) can easily be derived from the solid regression line in Fig. 3 by multiplying the ordinate with 0.6 and is shown by the broken line in Fig. 5: The average accumulation was about 0.26 µmol/min per g of fetal mass, i.e. about 21 µmol/min in a 80 g fetus.

The rate of **placental lactate transfer** at the end of the hypoxic period was determined from the uteroplacental blood flow and the arteriovenous concentration difference for lactate in the maternal blood passing through the pregnant uterus to be

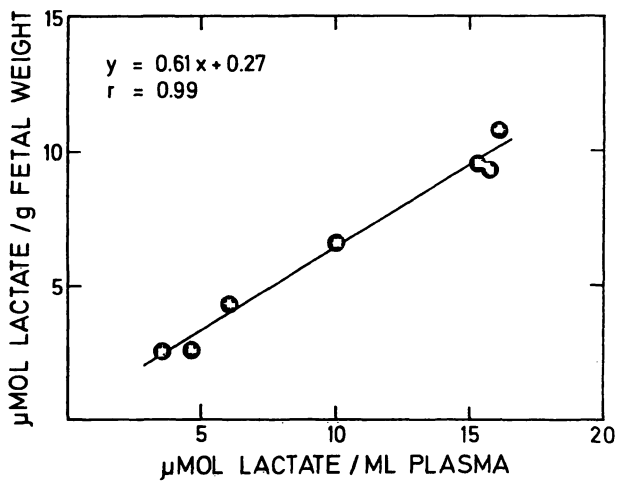

Fig. 4. Mean lactate concentration in the fetal body related to the plasma concentration.

Blood samples were drawn from the fetal carotid artery in order to determine the plasma lactate concentration. The anaesthetized fetus was rapidly removed from the uterus, weighed and placed into 500 ml 1 M perchloric acid with ice and homogenized within 1/2 min. The homogenate was centrifuged at 30.000 g for 20 min. The supernatant was filtered, brought to pH = 9.0 and centrifuged again. In the supernatant the lactate concentration was measured. From the concentration in the supernatant and the water content of the fetus (0.72 g/g) the mean body lactate concentration was calculated.

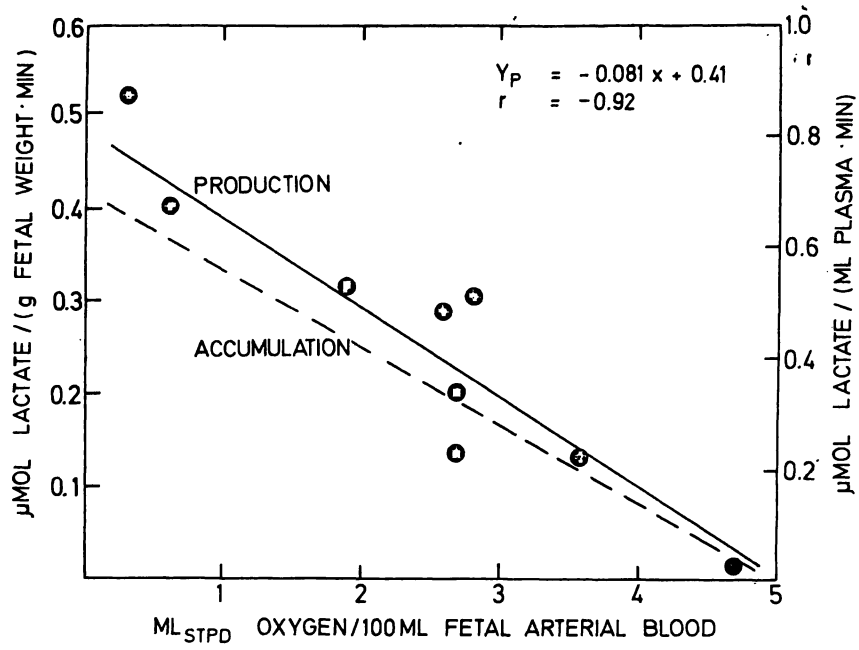

Fig. 5. Lactate production (closed circles, solid line) and lactate accumulation (broken line) in the fetal body related to the oxygen concentration in fetal arterial blood.

The distance between the two lines indicates the placental transfer. The placental transfer was determined from the placental clearance and the lactate concentration in maternal and fetal arterial plasma (n = 9).

3.3 µmol/min (SD = 2.9). A similar value for the placental transfer (3.9 µmol/min, SD = 1.4) has been calculated from the maternal and fetal arterial lactate concentrations and the placental clearance of lactate. Thus, the rate of placental transfer was about 17% of the rate of accumulation in the fetus. By summing up the lactate accumulation in the fetal tissue and the lactate transfer across the placenta, the **lactate production in the fetal body** is obtained. The lactate production is shown by the solid line and the closed circles of Fig. 5. It can be seen that **the amount of the produced lactate is about 15% higher than the amount of accumulated lactate**; the placental transfer slows down the rate of lactate accumulation to only a minor extent.

2.2 Disappearance, transfer, and utilisation of lactate during a normoxic period after a hypoxic period.

After the hypoxic period, the uteroplacental blood flow was adjusted to about its previous value. As shown in Fig. 2, the oxygen concentration in fetal arterial blood and the uterine O_2 uptake reached the previous levels. **In this posthypoxic normoxic period the fetal lactate concentration fell in an exponential way**: When the fetal lactate is considered that surpasses the maternal concentration of 4 µmol/ml the mean rate of lactate disappearance was 4%/min (SD = 2.8) in the first 10 min as well as in the second 10 min (SD = 2.0).

In Fig. 6, the single values of the lactate disappearance in the first 10 min are related to the fetal oxygen concentration. There is a highly significant correlation between the rate of disappearance (solid line) and the O_2 concentration in the fetal arterial blood.

The role of **placental transfer** played in the disappearance of lactic acid was evaluated as follows: As the arteriovenous lactate concentration difference was too small to be precisely measured, when maternal placental blood flow was normal, the transfer was determined only from the placental clearance and the fetomaternal concentration difference. This procedure seemed to be justified in view of the above agreement between the data obtained by this method and the other more direct method. The lactate transfer, given by eq. (1) was related to the amount of lactate accumul-

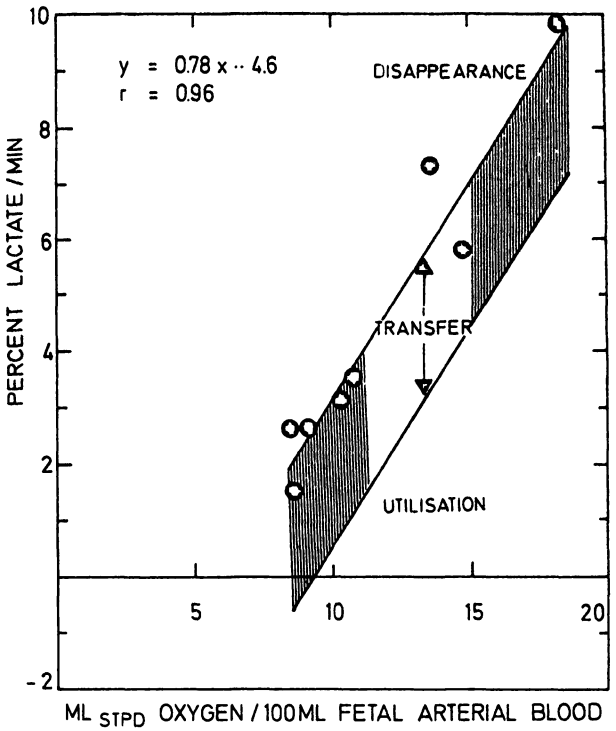

Fig. 6. Disappearance rate of lactate (closed circles, solid line) after a hypoxic period related to the oxygen concentration in fetal arterial blood.

The disappearance rate is calculated as rate of change of the lactate concentration per concentration difference between the fetal and maternal arterial plasma. According to the placental clearance the rate of lactate removal by placental transfer is 2.5% per min. The rate of removal by utilisation (broken line) is obtained by substracting these 2.5% per min from the disappearance rate.

ated in the fetus in excess to the maternal concentration. This ratio is given by the placental clearance (1.2 ml/min) divided by the fetal mass (80 g) and the fetal mean body concentration over the plasma concentration (0.6 ml/g) (see Appendix). The ratio indicates the rate of lactate disappearance by placental transfer; it is calculated to be 2.5%/min.

By substracting the rate of disappearance by placental transfer from the total rate of disappearance, the rate of disappearance by **utilisation** in the fetus was obtained (broken line in Fig. 6). **It is evident that lactate is utilised when the fetal arterial concentration surpasses 10 ml/100 ml (oxygen saturation 50%). The rate of utilisation rises with the oxygen concentration in fetal arterial blood.** The normal fetal oxygen saturation is probably about 60%, i.e. the oxygen concentration is 12 ml/100 ml. At this oxygen concentration the rate of lactate utilisation is 2.5%/min, and lactate is removed at equal rates by placental transfer and fetal metabolism. At lower oxygen concentration the transfer plays a dominant role, at higher concentrations the utilisation (Fig. 6).

Appendix

The amount of lactate (M_{EXC}) accumulated in the fetus in excess to the maternal concentration is given by the fetal mass, M_F, the concentration difference between maternal and fetal plasma (Δc) and the mean fetal body lactate concentration over the fetal plasma concentration (c_b/c_p):

$$M_{EXC} = M_F \,.\, \Delta c \cdot c_b/c_p \qquad (2)$$

The ratio R of the lactate transfer T and the amount of lactate M_{EXC} is derived from eq. (1) and eq. (2) to be:

$$\frac{T}{M_{EXC}} = \frac{\Delta c \cdot C}{M_F \cdot \Delta c \cdot c_b/c_p} = \frac{C}{M_F \cdot c_b/c_p} \qquad (3)$$

3 Conclusions

According to the present data the role of fetal metabolism and placental transfer during accumulation and disappearance of lactic acid may be assessed as follows: **During accumulation of lactic acid in hypoxic periods, metabolic lactic acid production is the dominant factor;** placental transfer of lactic acid diminishes the rate of accumulation to only a minor extent. **During lactic acid disappearance in posthypoxic normoxic periods, however, placental transfer and fetal utilisation of lactic acid are equally important.** Therefore, lactic acid concentration in maternal blood (affecting placental transfer) as well as the state of fetal oxygenation (affecting utilisation) must be taken into account in evaluating fetal acidosis after a period of hypoxia.

The lactic acid production in the fetus is related to fetal hypoxia in a similar way as the deceleration

of fetal heart rate: Both are inversely related to fetal arterial oxygen concentration. **The common relationship of lactic acid production and deceleration with the fetal oxygen concentration explains the correlation between fetal acidosis and the dip area of deceleration** [7, 11].

Summary

The present study was undertaken in order to measure, in a fetus with a hemochorial placenta, the rate of disappearance of lactate after hypoxia and to assess the role of fetal metabolism and placental transfer in these processes. The measurements were made at various fetal arterial O_2 concentrations.

Methods: Pregnant guinea-pigs near term were used. The preparation is shown in Fig. 1. Various fetal and maternal vessels were cannulated; the maternal carotid artery was shunted with the final portion of an uteroplacental artery via an electromagnetic flowmeter. The preparation allowed us to measure the uteroplacental blood flow and to induce fetal hypoxia and normoxia by varying uteroplacental blood flow. The lactate and oxygen concentrations in fetal and maternal blood were measured during and after reducing uteroplacental blood flow. The placental transfer of lactate was determined from the utero-placental blood flow and the arteriovenous concentration difference as well as from the placental clearance and the lactate concentrations in maternal and fetal arterial plasma.

Results: Accumulation, production and placental transfer of lactic acid during hypoxia.
When hypoxia was induced by reducing maternal placental blood flow an equivalent increase of lactate concentration and base deficit occurred in fetal plasma (Fig. 2). As shown in Fig. 3, the rate of lactate increase was related to the fetal oxygen concentration: It was about zero at a fetal concentration of 5 ml/100 ml (SO_2 = 25%); it reached a value of 0.7 μmol/(ml · min) at complete anoxia. The relationship between the lactate concentration in the fetal body and in the plasma was measured and is shown in Fig. 4. Using this relationship, the amount of lactate accumulating in the fetus was determined from the plasma lactate concentration as shown in Fig. 5. The amount of lactate transferred in the placenta was found to be about 15% of the lactate which was produced in the fetus, i.e. the rate of lactate accumulation was only slightly lower than the rate of fetal lactate production (Fig. 5).

Disappearance, utilisation and placental transfer of lactate during normoxia: When the reduction of uteroplacental blood flow was released the concentration of lactate in the fetus that was accumulated in excess to the maternal lactate concentration decreased in an exponential way. For an oxygen concentration of 12 ml/100 ml (SO_2 = 60%) the rate of disappearance was about 5%/min. **For this oxygen concentration the disappearance of lactate was caused to equal rates by placental transfer and fetal utilisation of lactate.** From the lactate disappearance and the lactate transfer the lactate utilisation was derived. As shown in Fig. 6 the rate of utilisation was directly related to the oxygen concentration in fetal arterial blood.

Conclusions: (1) **The rate of lactic acid accumulation during fetal hypoxia is determined almost exclusively by the rate of lactic acid production.** Placental transfer slows down the accumulation to only a minor extent. Lactic acid production by fetal tissue is inversely related to the O_2 concentration in fetal arterial blood. (2) **The rate of lactic acid disappearance during normoxic periods is equally due to metabolic utilisation and placental transfer.** The rate of lactic acid utilisation is directly related to the fetal arterial O_2 concentration.

Keywords: Acidosis, anoxia, fetus, hemochorial placenta, hypoxia, lactate, maternofetal exchange.

Zusammenfassung

Anstieg und Abfall von Laktat in Feten mit hämochorialer Plazenta. Die Bedeutung von plazentarem Transfer und fetalem Stoffwechsel
Ziel der Arbeit war es, bei Feten mit hämochorialer Placenta (Meerschweinchen) den Anstieg der Laktatkonzentration während Hypoxie und den Abfall der Laktatkonzentration nach Hypoxie zu messen und die Bedeutung des plazentaren Transfers und des fetalen Metabolismus bei diesen Prozessen abzuschätzen. Die Messungen erfolgten bei unterschiedlichen fetal-arteriellen O_2-Konzentrationen.

Methodik: Trächtige Meerschweinchen am Ende der Tragzeit wurden untersucht. Die Präparation ist in Abb. 1 dargestellt. Beim Muttertier wurden die A. carotis und die V. utero-ovarica kanüliert, beim Feten die A. carotis und die V. jugularis. Die materne A. carotis wurde über ein elektromagnetisches Flowmeter mit dem distalen Teil einer uteroplazentaren Arterie verbunden. Die Präparation ermöglichte, Proben des mütterlichen und fetalen Blutes zu entnehmen sowie die uteroplazentare Durchblutung zu messen und mit einer Klemme einzustellen. Durch Drosselung der uteroplazentaren Durchblutung bzw. durch Aufhebung der Drosselung wurden beim Feten Hypoxie bzw. Normoxie erzeugt. Unter diesen Bedingungen wurden die Laktat- und die O_2-Konzentration im fetalen und maternen Blut gemessen. Der plazentare Laktattransfer wurde 1) aus der uteroplazentaren Durchblutung und der arteriovenösen Konzentrationsdifferenz sowie 2) aus der plazentaren Clearance und den Lactatkonzentrationen im maternen und fetalen arteriellen Plasma bestimmt.

Ergebnisse: Anhäufung, Bildung und plazentarer Transfer von Laktat während Hypoxie: Bei fetaler Hypoxie erfolgte ein äquivalenter Anstieg der Laktatkonzentration im

Plasma und des Basendefizites im Extrazellularraum (Abb. 2). Wie Abb. 3 zeigt, ist die Geschwindigkeit des Laktatanstieges mit der fetalen Sauerstoffkonzentration negativ korreliert. Bei einer Sauerstoffkonzentration von 5 ml/100 ml (SO_2 = 25%) war der Konzentrationsanstieg nahezu Null; bei nahezu vollständiger Anoxie erreichte er einen Wert von 0,7 µmol/(ml · min). Die Beziehung zwischen mitlerer fetaler Laktatkonzentration und Plasmalactatkonzentration wurde durch Messungen im homogenisierten Feten und im Plasma bestimmt (Abb. 4). Unter Verwendung dieser Beziehung wurde aus dem Konzentrationsanstieg des Plasmalaktats während Hypoxie die Anhäufung von Laktat im Feten bestimmt (Abb. 5). Die plazentar transferierte Laktatmenge betrug 15% der im Feten gebildeten Laktatmenge; d. h. die Laktatanhäufung im Feten war nur geringfügig niedriger als die fetale Laktatproduktion (Abb. 5).

Abnahme, Abbau und plazentarer Transfer von Laktat während Normoxie: Während der posthypoxischen Erholungsphase fiel die Laktatkonzentration exponentiell ab. Bei einer Sauerstoffkonzentration von 12 ml/100 ml (SO_2 = 60%) betrug die Abnahme 5%/min. **Die Abnahme der Laktatkonzentration war gleichermaßen durch plazentaren Transfer und metabolischen Abbau im Feten bedingt.** Aus Laktat-Akkumulation und -Transfer wurde die Laktat-Utilisation bestimmt. Wie in Abb. 6 dargestellt ist, war die Abbaurate mit der Sauerstoffkonzentration im arteriellen Blut korreliert.

Schlußfolgerungen: (1) Der Konzentrationsanstieg von Milchsäure im Fetalblut während fetaler Hypoxie ist überwiegend durch die Milchsäureproduktion bestimmt; der plazentare Transfer beeinflußt die Anhäufung nur zu etwa 15%. Die Milchsäureproduktion im Feten wächst mit fallender Sauerstoffkonzentration im fetal-arteriellen Blut. **(2) Der Konzentrationsabfall der Milchsäure nach fetaler Hypoxie ist zu gleichen Teilen durch plazentaren Transfer und Abbau bestimmt.** Der Abbau der Milchsäure im Feten wächst mit steigender fetal-arterieller O_2-Konzentration.

Schlüsselwörter: Anoxie, Azidose, Fet, hämochoriale Plazenta, Hypoxie, Laktat, materno-fetaler Austausch.

Résumé

Accumulation et disparition du lactate dans un foetus avec placenta hémochorial.
Rôle du transfert placentaire et du metabolisme foetal

Dans notre présente étude nous avons tenté de mesurer chez les foetus avec placenta hémochorial (cobayes) la hausse de la concentration lactique pendant l'hypoxie et sa baisse après hypoxie et d'évaluer l'importance du transfert placentaire et du métabolisme foetal au cours de ces processus. Les mesures ont été effectuées sous diverses concentrations d'O_2 dans les artères foetales.
Méthode: Des cobayes gravides ont été examinés en fin de gravidité. La préparation est exposée Fig. 1. On a canulé chez la mère l'A. carotide et la V. utero-ovarienne et chez le foetus l'A.carotide et la V. jugulaire. L'artère carotide maternelle a été reliée par flowmeter électromagnétique avec la partie distale d'une artère uteroplacentaire. La préparation a permis de prélever des échantillons du sang maternel et foetal ainsi que de mesurer l'arrosage sanguin utéroplacentaire et de le stopper par une pince. Le stoppage et la remise en route de l'irrigation sanguine ont provoqué respectivement une hypoxie et une normoxie chez le foetus, pendant lesquelles on a mesuré la concentration de lactate et d'O_2 dans le sang foetal et maternel. Le transfert de sel lactique placentaire a été évalué (1) à partir de l'arrosage sanguin utéroplacentaire et de la différence de concentration artérioveineuse ainsi qu'à partir (2) de la clearance placentaire et des concentrations lactiques dans le plasma artériel maternel et foetal.
Résultats: Accumulation, formation et transfert placentaire du lactate pendant l'hypoxie: En cas d'hypoxie foetale, on a pu observer une augmentation proportionnelle de la concentration lactique dans le plasma et du déficit basique dans la zone extracellulaire (Fig. 2). Ainsi qu'on peut le voir Fig. 3, la vitesse d'augmentation lactique est en corrélation négative avec la concentration d'oxygène foetale: La hausse de concentration a été pratiquement nulle pour une concentration d'oxygène de 5 ml/100 ml (SO_2 = 25%), et a atteint une valeur de 0,7 µmol/(ml · min) pour une anoxie presque complète. La relation entre la concentration lactique foetale moyenne et la concentration lactique du plasma a été analysée par des mesures dans le foetus homogénisé et dans le plasma (Fig. 4). Utilisant cette relation, nous avons établi à la suite de la hausse de concentration du lactate du plasma pendant l'hypoxie l'accumulation de lactate dans le foetus (Fig. 5). La quantité de lactate placentaire transférée représentait 15% du lactate formé dans le foetus, ce qui signifie que l'accumulation de lactate dans le foetus n'a été que de très peu inférieure à la production de lactate foetal (Fig. 5).

Décroissance lactique, catabolisme et transfert placentaire pendant la normoxie: Durant la phase de rétablissement post-hypoxique, la concentration de lactate baisse de façon significative. Cette baisse fut de 5%/min pour une concentration d'oxygène de 12 ml/100 ml (SO_2 = 60%); elle fut conditionnée à part égale par le transfert placentaire et le catabolisme dans le foetus. **L'utilisation lactique a été déterminé à partir de l'accumulation et du transfert de lactate.** Ainsi qu'on peut le voir Fig. 6, il existe une corrélation entre le taux de catabolisme et la concentration d'oxygène dans le sang artériel.

Conclusions: 1) La hausse de concentration du lactate dans le sang foetal pendant l'hypoxie foetale dépend surtout de la production lactique; l'influence du transfert placentaire sur l'accumulation ne dépasse pas 15% environ. La production lactique dans le foetus augmente à mesure que diminue la concentration d'oxygène dans le

sang artériel du foetus. 2) **La baisse de concentration du lactate aprés hypoxie foetale est déterminé à part égale par le transfert placentaire et le catabolisme.** Le catabolisme du lactale dans le foetus croît parallèlement à la hausse de concentration d'O_2 dans le sang artériel du foetus.

Mots-clés: Acidose, anoxie, échange materno-foetal, foetus, hypoxie, lactate, placenta hémochorial.

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